

# Fruits and vegetables in disease prevention: a global perspective

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'In primitive times, lack of food gave languishing bodies to death; now, on the other hand, it is abundance buries them.' [Lucretius, 50 BC]

The diet and cancer story is complex, if only because there are a large number of cancers of different types and sites. Further complexity has been created by the fact that different approaches to the study of cancer have been taken by scientists from separate disciplines. What is presented here is a synthesis of findings from epidemiological and experimental research. When the National Academy of Science (NAS) report on diet and cancer was published in 1982<sup>1</sup>, many of the data that were available were derived largely from animal studies and from descriptive and ecological epidemiology. During the 1980s and 1990s, a great deal of evidence accumulated from epidemiological studies at the individual level – both cohort and case–control studies. Much of this work identified relationships between aspects of diet and cancer that provided more detail but was not markedly inconsistent with the earlier conclusions. What has changed is a reduction of the focus on traditional macro- and micronutrients in favour of specific bioactive components, whole foods and dietary patterns<sup>1</sup>.

In order to better understand the relationship between food and cancer and to quantify the extent to which cancer is a largely preventable disease, the World Cancer Research Fund and the American Institute for Cancer Research commissioned a panel of experts chaired by this author to explore a global perspective on these issues. Our findings were published in the report, *Food, Nutrition and the Prevention of Cancer: a Global Perspective*<sup>2</sup>, from which these remarks are taken. The words 'convincing', 'probable' and 'possible' were used to describe the degree to which the panel regarded the associations seen as potentially causal. They are defined clearly in the report.

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Most epidemiological studies on vegetables, fruits and cancer risk have been case-control studies but the number of cohort studies has recently grown. A few ecological studies, mostly based on food balance data, provide additional evidence. Some animal experimental studies have entailed the feeding of vegetables and fruits as such (not just individual micronutrients or other bioactive compounds) and have examined the resultant tumour incidence or some intermediate outcome. To date, no human feeding trials in which cancer incidence was the measured outcome have been undertaken using vegetables and fruits, because of the length of time and number of participants necessary to accrue enough cases for assessing the effect with appropriate statistical power. There are some trials of this sort underway now, however.

Despite these difficulties, perhaps the most important finding that has emerged strongly in recent years is that diets high in vegetables and fruits (and therefore in fibre, antioxidants and other bioactive microconstituents) are associated with reduced risk of most, if not all, epithelial cancers<sup>3,4</sup>.

## Establishing the evidence

Establishing the inverse relationship between increased fruit and vegetable consumption and reduced cancer risk is a task complicated by several factors, notably measurement issues, inconsistencies in classifications and a variety of confounding factors.

One problem with the measurement of vegetable and fruit consumption is a tendency towards overestimation of intake with self-reporting<sup>5-7</sup>. This may be due to 'social desirability bias', perhaps particularly in societies where vegetables and fruits are deemed 'healthy foods'. It is further possible that a selection bias occurs in some studies so that both cases and controls are of higher socioeconomic status than the general population and, therefore, have an actual intake that is somewhat higher than the population average.

Inconsistencies in vegetable and fruit classification schemes also make a summary of the data, as a whole, complicated. In some studies, vegetables and fruits have been categorized according to botanical classification; in others, categorization has been according to culinary usage. Some studies have included legumes (pulses) as vegetables, whereas others have classified these as a separate entity, or not at all.

Another difficulty in data interpretation arises from the failure to report null findings. Some studies that have reported results for only a few vegetable and fruit items have probably also found null associations for other items, but have not included these results in their publication.

Some studies have analysed data for a large number of vegetable and fruit items, thus increasing the probability of finding a significant association for one or a few items due to chance alone. In evaluating the contribution of multiple comparisons to the evidence for a potentially protective effect of vegetables and fruit, it should be noted that, as a point of reference, multiple comparisons have also been made in many studies for other food groups, perhaps particularly for cereal (grain) products; it is noteworthy that far fewer statistically significant associations have been observed than is true for vegetables and fruits.

Most case-control and cohort studies of vegetable and fruit consumption have been conducted within populations that have relatively homogeneous diets; this makes discussion of wider ranges of intake speculative. However, odds ratios or relative risks representing weak inverse (potentially protective) associations for vegetables and fruits from these studies may in fact be signalling stronger associations for greater differences in intakes. Ecological studies (across countries or cultures) are useful for making comparisons across a wider range of intakes, although attention must be given to the many potentially confounding factors that also vary across populations.

Potential confounders must also be considered in the interpretation of results from case-control and cohort studies. Levels of certain known cancer risk factors may vary systematically with vegetable and fruit consumption (at least in some cultures), and the possibility that observed associations are not causal, but rather explained by other associated factors, must be evaluated. In particular, smokers have been documented to consume fewer vegetables and fruits than non-smokers<sup>8,9</sup>. Further, dietary fat intake has been shown to be inversely correlated with vegetable and, particularly, fruit intake in the USA<sup>10</sup>. Evaluation of the degree to which these factors are responsible for observed associations for the consumption of vegetables and fruits is important in studies of cancers thought to have tobacco- or dietary fat-related aetiologies. Most recent studies of the effects of fruits and vegetables in cancers thought to be caused by smoking have attempted to control for the effect of smoking. Physical activity, age, socioeconomic status and alcohol intake are other factors that may correlate with intakes of vegetable and fruits, and the role of these should likewise be evaluated.

Although the issue of confounding must be considered seriously, it is impressive to note that more than 200 epidemiological studies have been conducted in quite diverse populations, in which health-related behaviours do not always cluster in the same way. Thus, no single correlate of vegetable and fruit consumption is likely to explain the consistent finding of inverse (potentially protective) associations across many sites and many populations.

## Evidence of reduced risk of cancer

Vegetables and fruits are relatively rich in vitamins, minerals and other bioactive compounds compared with other food groups. Although different types have different nutrient profiles, they are, generally, good sources of non-starch polysaccharides (NSP)/fibre, carotenoids, vitamin C, folate, potassium and other vitamins, minerals and bioactive compounds. Some specific vegetables are good sources of B vitamins, calcium and iron. Dried fruits are concentrated sources of energy, sugar, dietary fibre and iron.

The literature on vegetables, fruits and the prevention of cancer has been reviewed in several scientific papers, including those by Steinmetz and Potter<sup>3,4,11</sup>, Block *et al.*<sup>12</sup> and Ziegler<sup>13</sup>. In 1991, Steinmetz and Potter examined 137 epidemiological studies and concluded that 'consumption of higher levels of vegetables and

fruit is associated consistently, although not universally, with a reduced risk of cancer at most sites', and that the association was 'most marked for epithelial cancers – particularly those of the alimentary and respiratory tracts ...'.

In a 1992 review, Block *et al.*<sup>12</sup> found a statistically significant inverse (potentially protective) association 'with fruit and vegetable consumption ... in 128 of 156 dietary studies in which results were expressed in terms of relative risk'. At least 37 cohort, 196 case-control and 14 ecological studies have investigated the relationship between vegetable and fruit consumption and the risk of cancer. The case-control evidence is most abundant and consistent for cancers of the stomach, oral cavity, lung, oesophagus, pancreas and rectum: 80% of studies have shown a statistically significant inverse (potentially protective) association for each of these sites for one or more vegetable and/or fruit categories (Table 1).

**Table 1** Vegetables and fruits and cancer risk. In the judgement of the WCRF panel, vegetables and fruits modify the risk of cancers of various sites as shown; judgements are graded according to the strength of the evidence<sup>2</sup>

Evidence	Decreases risk	No relationship*	Increases risk*
Convincing	<i>Vegetables and fruits</i> Mouth and pharynx Oesophagus Lung Stomach <i>Vegetables</i> Colon, rectum	–	–
Probable	<i>Vegetables and fruits</i> Larynx Pancreas Breast Bladder	–	–
Possible	<i>Vegetables and fruits</i> Cervix Ovary Endometrium Thyroid <i>Vegetables</i> Liver Prostate Kidney	–	–

\* There are no cancer sites for which the current evidence suggests either a null association or increased risk with higher intakes of vegetables or fruit.

Raw vegetables: convincing for stomach.

Green vegetables: convincing for lung and stomach; probable for mouth and pharynx; possible for oesophagus; convincing for breast.

Cruciferous vegetables: probable for colon, rectum and thyroid.

Allium vegetables: convincing for stomach; possible for colon.

Carrots: probable for lung, stomach and bladder; possible for oral and rectum.

Tomatoes: convincing for stomach; possible for lung.

## Summary of evidence by cancer site

### Mouth, pharynx and oesophagus

Smoking (or other tobacco habits) and high alcohol consumption are thought to be of major importance in causing cancer in these sites, and many studies have performed appropriate statistical adjustments to allow for these factors. Inverse associations with fruit and vegetable consumption remained in the great majority. For cancer of the mouth and pharynx, the evidence of an inverse (potentially protective) association is most consistent for carrots, citrus fruit and green vegetables, but the evidence for vegetables and fruits in general is convincing.

For oesophageal cancer, the evidence for an inverse association for vegetables in general, and for tomatoes and citrus fruits, was entirely consistent in one cohort and 22 case-control studies, and statistically significant inverse associations have been found for at least one vegetable/fruit category in 18 studies. Overall, the evidence that vegetables and fruits protect against oesophageal cancer is convincing.

### Lung

Lung cancer is one of the sites for which the most prospective data are available; six cohort studies and 13 case-control studies have examined consumption of vegetables and fruits in the context of lung cancer. In these studies, the associations with intake of vegetables and fruit were appropriately adjusted for cigarette smoking. This reduces the possibility of observing a false protective association as a result of non-smokers consuming more vegetables and fruit than smokers, a phenomenon that has been documented in various populations<sup>9,10</sup>.

Inverse (potentially protective) associations were consistently shown for vegetables and fruits together and separately, and with individual items in both categories, in both cohort and case-control studies. The evidence for vegetables, fruit, green vegetables and tomatoes is convincing; six out of seven studies have also found inverse associations for carrots.

### Stomach

Stomach cancer is the cancer most studied with respect to the consumption of vegetables and fruits. Six prospective cohort studies and 32 case-control studies have focused upon this site. Inverse (potentially protective) associations with vegetables and fruits, collectively and separately, and with at least one fruit and/or vegetable category have been consistent. Most studies adjusted for potential confounding factors. Evidence that vegetables and fruits protect against stomach cancer is convincing.

## **Colon and rectum**

Evidence from four prospective studies that examined consumption of vegetables and fruits in relation to the risk of colon cancer was more consistent for vegetables than fruits. Evidence of an inverse (potentially protective) association is stronger for women than men. A majority of the case–control studies showed a significant inverse association for at least one vegetable and/or fruit category, and such associations were particularly consistent for raw and green vegetables. Findings for fruit consumption and colon cancer risk are less abundant; two studies found increased risk with higher intakes and one decreased risk, while the majority showed no association. There is only one prospective study on rectal cancer, but evidence from case–control studies was most consistent for cruciferous vegetables, carrots and citrus fruit, which all appear to be protective against rectal cancer. Overall, evidence on vegetables showed inverse associations, while risk for fruits was inconsistent. There is also some evidence that consumption of vegetables and fruits may decrease the risk of developing adenomatous colorectal polyps. Evidence that vegetables decrease the risk of colon and rectal cancer is convincing.

## **Larynx**

Evidence from case–control studies generally suggests that increased consumption of vegetables and fruits is linked to decreased risk of cancer of the larynx. Most studies controlled for tobacco smoking and alcohol. However, the number of studies overall is limited, not all have shown statistically significant findings, and there are few data on specific vegetables and fruits. Vegetables and fruits probably protect against laryngeal cancer.

## **Pancreas**

The three prospective cohort studies of pancreatic cancer showed both increased and decreased risks for vegetables or fruit, although none of the associations was statistically significant. Evidence from 10 case–control studies was more consistent, with nine reporting a statistically significant association for one or more vegetable and/or fruit categories. Data on specific types of vegetable and fruit categories are limited. All the case–control studies used some surrogate respondents, due to the very short survival time of the disease. Notably, many of the studies did not adjust for tobacco smoking. Vegetables and fruits probably protect against pancreatic cancer. More prospective data would be helpful.

## **Breast**

Two out of the three prospective cohort studies have reported lower relative risks for higher vegetable consumption and one found a similar result for fruit intake. While

evidence from 19 case–control studies was also informative, with 10 finding a statistically significant inverse (potentially protective) association for one or more vegetable and/or fruit categories, the majority of these studies did not adjust the associations for fat intake. Eight of 11 studies on vegetables as a general category, but only four of 12 studies on fruits, found inverse associations. Six of the studies on fruits found null associations. A study that examined women after surgery for early breast cancer found more favourable prognostic tumour characteristics in those who had previously eaten more fruit and vegetables. Vegetables and fruits probably protect against breast cancer.

## **Bladder**

Five cohort studies that reported on vegetables and fruits and the risk of bladder cancer found either decreased risk or no association for vegetables and fruits combined or various categories of vegetables or fruits. Of nine case–control studies that reported on statistical significance, eight found inverse associations for one or more vegetable and/or fruit categories. Carrots and green vegetables are the specific categories that have been most often examined and results have consistently shown an inverse (potentially protective) association. The majority of the studies adjusted for cigarette smoking (or found equivalent associations within both smokers and non-smokers); this is recognized to be the most important risk factor for bladder cancer. Vegetables and fruits probably protect against bladder cancer.

## **Ovary**

Six case–control studies have reported inverse associations for one or more vegetable and/or fruit groups. While most studies have investigated only a limited number of vegetable or fruit categories, associations have largely been inverse. The evidence indicates that vegetables and fruits possibly protect against ovarian cancer.

## **Endometrium**

Five case–control studies of vegetable and fruit intake and endometrial cancer have been reported. Of these, four have observed inverse associations for one or more vegetable and/or fruit categories. Three have reported inverse associations for fruit, and two for carrots; data are not abundant for other specific types of vegetables or fruit. Odds ratios of 0.5 or lower have been reported for various vegetables or fruit in four of the five studies. Vegetables and fruits possibly protect against endometrial cancer.

## Cervix

While a prospective cohort study in Japan reported an inverse association between green and yellow vegetable consumption and the risk of cervical cancer, evidence from case–control studies is less clear-cut. Four found inverse associations for one or more vegetable and/or fruit categories but few data are available on any individual category of vegetables or fruit. Such findings as there are tend to be inconsistent. Three out of four case–control studies of women with *in situ* cervical cancer or cervical dysplasia did not produce clear evidence of a protective role for vegetables and fruit, although associations have been found for some specific items. Vegetables and fruits possibly protect against cervical cancer.

## Thyroid

Five case–control studies of cancer of the thyroid have reported statistically significant inverse associations for one or more vegetable and/or fruit categories. All five studies reported inverse (potentially protective) associations for cruciferous vegetables, although in one study this applied to women only. It is interesting that, as well as containing several plausibly anticarcinogenic substances, cruciferous vegetables carry compounds which may promote goitre development and which have been shown to cause thyroid cancer in animal experiments. While there is no good evidence that goitrogenic compounds are harmful in iodine-sufficient areas of the world, they may contribute to goitre in areas where iodine deficiency occurs. Vegetables and fruits possibly decrease the risk of thyroid cancer.

## Liver

Three cohort studies and five case–control studies have examined vegetable intake and liver cancer. All three cohort and the majority of the case–control studies found decreased risk with higher intakes. A cohort study in Japan has shown decreased risk of liver cancer with greater green and yellow vegetable intake. Evidence relating to fruit consumption is limited. Diets high in vegetables possibly decrease the risk of primary liver cancer.

## Prostate

Evidence from epidemiological studies on vegetables and fruits and the risk of prostate cancer is less consistent than for other sites. Two of seven cohort studies found no association for all vegetables and fruits, the other five studies reported various associations for different categories of fruits and vegetables and most were inverse (potentially protective) or null. Most case–control studies reported null associations for vegetable and fruit consumption, with a few studies showing increased



risk with higher consumption of fruits. Vegetables possibly decrease the risk of prostate cancer.

## **Kidney**

One cohort study found no association between renal cancer mortality and vegetable consumption. The five case-control studies of renal cell carcinoma that have examined vegetable and fruit consumption controlled for cigarette smoking and obesity. Three studies found a statistically significant inverse association for at least one vegetable and/or fruit category and weak inverse associations were found for the majority of vegetable and fruit categories examined. The available evidence suggests that vegetables possibly protect against renal cancer.

## **Evidence of increased risk of cancer**

There is no cancer site for which the evidence, taken as a whole, supports an overall increase in risk with higher intakes of vegetables and fruits (Table 1). As far as cancer as a whole is concerned, there is a theoretical possibility that consumption of vegetables and fruits might increase risk because of the presence of certain microconstituents or contaminants. These may include goitrogens, nitrates from fertilizer residues, naturally contained nitrates, pesticide residues and aflatoxin contamination.

Nitrate is present in large quantities in vegetables. However, concomitant intake of various antioxidants in fresh vegetables probably prevents oxidation of nitrate to nitrite and counteracts any risk of cancer<sup>14</sup>. There is no good evidence that nitrate from vegetables increases cancer risk.

Some pesticides are known to be toxic. In most developed countries, use of pesticides believed to be harmful is regulated, but this is much less true in the developing world. In any case, all foods of animal and plant origin include contaminant residues; vegetables and fruits are not especially problematic in this respect. There is no evidence at present that any vegetables and fruits, which have been properly stored and cleaned, have any significant adverse health effects.

## **Significance of plant foods for preventing other diseases**

There is good evidence that diets high in vegetables and fruits protect against a number of diseases other than cancer. Carotenoids, vitamin C and perhaps other antioxidants protect against cataracts. They also decrease the oxidation of cholesterol in the arteries and thus potentially protect against cardiovascular disease. Vitamin C may help maximize intestinal iron absorption and thus help prevent iron deficiency anemia. In some developing countries, where food is scarce or diets are monotonous, the inclusion in the diet of even small amounts of vegetables and fruits containing  $\beta$ -carotene and vitamin C help prevent xerophthalmia and scurvy.

Many vegetables and fruits are high in NSP/fibre, and most are high in potassium. NSP/fibre may help control diabetes and high serum cholesterol levels, and protects against diverticular disease and other digestive disorders. Potassium may help prevent or control hypertension and thereby reduce the subsequent risk of stroke and heart disease. Vegetables and fruits contain very little fat, and are low in calories. (Avocados are one exception, and drying, of course, increases the energy content of fruits.) Diets high in vegetables and fruits can therefore protect against obesity and thus against the risk of cardiovascular disease, as well as against those cancers associated with being overweight and obese.

The World Health Organization report, *Diet, Nutrition and the Prevention of Chronic Diseases*<sup>15</sup> recommended a goal of at least 400 g of vegetables and fruits daily (in addition to potatoes) including, within that, at least 30 g of legumes, nuts and seeds. Of 100 expert reports published between 1961 and 1991 that were mostly concerned with diet and cardiovascular diseases or diet and chronic diseases, 66 recommended higher consumption of vegetables and 66 recommended higher consumption of fruits, with none disagreeing<sup>16</sup>.

## Public policy: some earlier recommendations

Although the very earliest epidemiological studies of diet and cancer suggested a lower risk with higher intake of vegetables and fruits, the concept that diets rich in vegetables and fruits protect against cancer did not receive much consideration until the 1980s. The 1982 NAS report, *Diet, Nutrition and Cancer*<sup>1</sup>, included a guideline emphasizing 'the importance of including fruits, vegetables, in the diet'. The report reviewed the evidence on various micronutrients, including  $\beta$ -carotene, vitamin C, vitamin E and selenium, but did not summarize the literature on vegetables and fruit as such.

The later NAS report, *Diet and Health*<sup>17</sup>, concluded that diets high in plant foods, including vegetables and fruits, 'are associated with lower occurrence of coronary heart disease and cancers of the lung, colon, esophagus, and stomach' and, referring in particular to the evidence on vegetables and fruits and cancer, recommended five or more daily servings of a combination of vegetables and fruits, especially green and yellow vegetables and citrus fruits.

In 1992, the 5 A Day for Better Health Program was launched by the National Cancer Institute in the USA, with the goal of increasing average vegetable and fruit consumption to at least five servings per day by the year 2000<sup>18</sup>. Several other countries have implemented similarly designed programmes aimed at decreasing disease risk through increasing fruit and vegetable consumption.

## Changing consumption and cancer patterns

As populations shift their dietary patterns from ones that rely heavily on locally grown and/or available foods to increasingly manufactured foods, cancer rates may

change dramatically. For example, in most populations in the developed world, stomach cancer has been declining rapidly in recent decades, whereas rates of cancers of the colon, breast and prostate have been rising. Further, variations in cancer patterns are seen in studies of migrants. Additionally, patterns of cancer are now changing rapidly within the economically developing world as populations age and become increasingly industrialized and urbanized. Such variations with time, migration and urbanization indicate that cancer rates are strongly influenced by environmental factors, including diets, and that cancer is therefore largely preventable.

Dietary patterns have evolved throughout history and vary greatly in different parts of the world. In rural areas of economically developing countries, diets may depend solely on what a family or local community produces. As the use of cash is extended, a greater variety of foods becomes available in local markets or shops. In economically developed societies and in the urban areas of developing countries, diets are a reflection, not only of food supplies grown and manufactured locally, but also of those available nationally and internationally and, ultimately, of market economies that ensure the availability of a wide range of manufactured foods, that, none the less, may paradoxically be derived from a limited variety of primary foods.

## **Human dietary variation: towards a protective diet**

The diets typically consumed in rural areas of Africa, Latin America, Asia and Oceania often still rely on one or two staple cereal foods and may be fairly monotonous and bulky. Mostly, cereals are dominant, especially in the low-income countries of Asia, as well as in China and India. Rice dominates in Asia, wheat in North Africa, maize (corn) in Latin America, and maize and starchy roots in sub-Saharan Africa.

Foods of animal origin and added fats are eaten only occasionally in rural areas, exceptions being gatherer–hunter and pastoral communities, and populations who live by rivers and oceans. Vegetables and fruits do not occupy a very important place in the diet. These diets include few industrially processed foods – such products are locally unavailable, or else beyond the reach of people living in subsistence economies.

As countries develop economically, consumption of the dominant staple cereal foods declines. The amount of fats and oils consumed tends to rise sharply. There is a consistent fall in the overall consumption of foods of plant origin and a replacement with increasing amounts of foods of animal origin, notably meat, meat products and dairy products. Sugar consumption also generally increases rapidly. Because, as a function of industrialization and urbanization, diets contain relatively more food of animal origin, and relatively fewer foods of plant origin, such diets are correspondingly lower in the bioactive compounds found in food of plant origin. An ever increasing proportion of food in industrialized societies is processed.

Within some of the most economically developed countries, this process has slowed and, for some population subgroups, it has reversed. Southern Europeans continue to consume more red meat, total fats and sugar, but there is now a discernible trend in some northern European countries and within North America

towards an increasing consumption of vegetables and fruits and a somewhat decreasing consumption of red meat, fat, full-fat milk, other dairy products, and sugar in the form of sucrose. This shift is most noticeable in countries where messages about nutrition and public health have been accepted by governments and promoted by health authorities and in the media.

## A call to action

A major recommendation of the World Cancer Research Fund and American Institute for Cancer Research report is that prevention of 30–40% of cancers worldwide by dietary and associated means (including exercise and weight management – but also protecting the food supply from contamination, a particular problem in the developing world) is achievable<sup>2</sup>. Currently, vegetables and fruits provide less than 5% of the total energy in most areas of the world. In some areas of China, Oceania and the Caribbean, vegetables and fruits provide over 10% of the total energy; in southern Europe they provide about 6% of the total energy. Industrialized diets average about 5% of the total energy from vegetables and fruits. Consumption is lowest in parts of Eastern Europe and in the poorer countries of Africa and Asia.

Diets that are aimed at reducing chronic disease are important in the developed world, but crucial in the developing world. Treatment of cancer in developing nations, even by 2010 for some countries, could consume the entire national health budget. Prevention, started now, is the only solution to even beginning to control this looming problem.

Recommendations are for 7% of total energy intake to come from vegetables and fruits, which is 400–800 g day<sup>-1</sup> (at least five servings a day). Success requires key sectors in society to work in collaboration to achieve potentially protective patterns of dietary change, especially increasing fruit and vegetable consumption. Strategies to reduce the incidence of cancer should complement and not compete with the strategies to reduce the incidence of other major diseases. Action to prevent cancer is rational, timely and important, and should, therefore, be a major priority and responsibility for all agents of societal and individual change, including international agencies, governments, industry, non-governmental organizations, medical and health authorities, consumer and public interest groups, and the media.

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